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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/501,028	03/14/2005	Christopher M. Starr	15021-6	1759

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EXAMINER	
SRIVASTAVA, KAILASH C	
ART UNIT	PAPER NUMBER
1657	

MAIL DATE	DELIVERY MODE
08/17/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/501,028	STARR ET AL.	
	Examiner	Art Unit	
	Kailash C. Srivastava	1657	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 April 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-9 and 11-29* is/are pending in the application.

4a) Of the above claim(s) *6,15 and 21-29* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,7-9,11-14 and 16-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Response, amendments and remarks filed 28 April 2009 to Office Action mailed 29 October 2008 is acknowledged and entered.

Informal Matters

Declaration from Dr. Wilfred Jeffries under 37 C.F.R. §1.132 filed 28 April 2009 is acknowledged, entered, and considered in the Office Action that follows below.

For the record, please further note, applicants elected on record the species of β-hexosaminidase A as the protein, whose deficiency causes the lysosomal storage disease (See Applicant's response, filed 08 November 2007, wherein an election without traverse was made to prosecute the species:

i. Sandhoff disease from Claim 12; and;

ii. β-hexosaminidase A as the protein from Claims 13 and 20.

Withdrawals of Rejections

In view of applicants' remarks and amendment filed 28 April 2009, following rejections in the Office Action mailed 29 October 2008 are hereby withdrawn:

- Indefiniteness rejection to Claims 9, 11 and 19 under 35 U.S.C. §112, second paragraph; and

- obviousness rejection to Claims 1-5, 7-14 and 16-20 under 35 U.S.C. §103(a) as obvious over the combined teachings from LeBowitz (USPGPB 2003/0072761 A1) and DeFrees et al. (U.S. Patent 7,138,371 B1) in view of Jeffries et al (US Patent 5,981,194).

Claims Status

Claim 10 is currently cancelled.
Claims 1-9 and 11-29 are currently pending.

Claims 6, 15 and 21-29 remain withdrawn.

Claims 9, 11 and 19 have currently been amended.

Claims 1-5, 7-9, 11, Sandhoff disease in Claim 12, β-hexosaminidase A as the protein Claimed in Claim 13, Claims 14, 16-19 and β-hexosaminidase A as the claimed protein in Claim 20 are examined on merits.

Note, Claims 6 and 15 were withdrawn in the Office Action mailed 29 January 2008 and subsequently again in the Office Action mailed 29 October 2008. However, in the identifiers for the Claims 6 and 15 in the amendment filed 28 April 2009, Claims 6 and 15 have still been identified as "Original". Accordingly, Claims 6 and 15 do not conform to the proper identifiers requirement under 37. CFR §1.121 (See, M.P.E.P. §714 [R-5] c). In response to the instant Office Action, please ensure that the claims identifiers correctly reflect the Claim status.

Election/ Restriction

Regarding arguments that Claims 6 and 15 should also be considered along with Claims 1-5, 7-14 and 16-20 rather than withdrawing Claims 6 and 15 from further consideration; said withdrawal is based on applicants' election as presented in the response filed 08 November 2007, wherein an election without traverse was made to further prosecute Group I invention encompassing Claims 1-20, consisting of:

- Claims 1-13 drawn to a method to treat a subject having a lysosomal storage disease by administering to said subject a composition comprising a p97 molecule covalently linked to a protein;
- consisting of Claims 14-20 drawn to a p97 molecule covalently linked to a protein; and
- additional election of following species:
    i. Sandhoff disease from Claim 12; and
    ii. protein- β-hexosaminidase A from Claims 13 and 20.

Accordingly, all other species mentioned in Claims 12-13 and 20 were withdrawn from further consideration. Note, each of Claims 6 and 15 is drawn specifically to α-L-iduronidase, a non-elected species. Additionally, as mentioned *supra* applicants election detailed above was without traverse and has been made Final in Office Action mailed 08 November 2007.

Since applicants have received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits, which is why each of Claims 6 and 15 remain withdrawn from consideration as being directed to a non-elected invention. See 37 CFR §1.142(b) and MPEP § 821.03.

Claim Rejections - 35 U.S.C. §112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. §112:

> ***The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.***

Claims 1-5, 7-14 and 16-20 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while enabled (See, e.g., Examples 1-5) for:

- localization of p97 in a cell;
- preparation of p97 linked to a fluorescent marker for its detection in a cell having lysosome;
- preparation of compositions comprising p97 linked to a protein for its administration to a patient;
- potential modes (i.e., oral or other) to administer said compositions to a patient in need thereof, i.e., suffering from a lysosomal disease; and
- evaluation methods to determine the efficacy of said administration in a patient;

is not enabled for a method to treat a subject having a lysosomal storage disease comprising a method wherein a composition comprising a p97 molecule covalently linked to a protein is actually administered to said subject/patient.

In response filed 28 April to the above-recited rejection to Claims 1-5, 7-14 and 16-20 in the Office Action mailed 29 October 2008, the presented arguments are that even in the absence of providing evidence that the instantly Claimed method invention of treating a subject having a lysosomal storage disease by administering a composition comprising a p97 molecule covalently linked to a protein whose deficiency causes the disease; said method is enabled (Remarks filed 28 April 28, 2009, Page 7, Lines 31-38) because in examples 1-2 of the currently presented specification and further according to the Declaration from Dr. Jeffries, the inventors have demonstrated that the p97 is capable of targeting its conjugated partner in to the lysosome of a cell and further, p97 has previously been demonstrated to deliver compounds through the blood brain barrier (i.e., BBB). Applicants also argue that the pertinent literature information shows that the lysosomal enzyme replacement therapy is the basis to treat the

lysosomal storage disease (Remarks filed 28 April 28, 2009, Page 7, Lines 39-40 and Page 8, Lines 4-6). Applicants have additionally argued that the instantly claimed method is an improvement over the previously known treatment methods because the lysosomal enzyme is delivered to the lysosome of the cell (Remarks filed 28 April 28, 2009, Page 8, Lines 5-6). Applicants also argue that contrary to Examiner's rejection regarding the preparation of a p97-protein conjugate; at Paragraphs 10-11 of the declaration, Dr. Jeffries shows that p97-N-iduronidase conjugates were made and the results at paragrah 11 show that said complex co-localizes in the cellular lysosome (Remarks filed 28 April 28, 2009, Page 8, Lines 13-19). Yet another argument that the applicants present is that the Examiner alleges that a number of pharmacokinetic variables/parameters have neither been determined, nor suggested, but applicants again submit that said information are neither necessary, nor required for enablement because said information can only be obtained through clinical trials and would therefore be unfair on Examiner's part to require said information to demonstrate enablement of the claimed invention (Remarks filed 28 April 28, 2009, Page 8, Lines 13-25) and lastly , Applicants have demonstrated that a fusion protein can be delivered to the target cell with intact activity because at paragraph 12 of the Declaration. Dr. Jeffries shows that the p97 is degraded with cathepsin D laving the lysosomal enzyme intact and biologically active ((Remarks filed 28 April 28, 2009, Page 8, Lines 25-30).

First of all, Applicants' claim a method to treat a subjected having a lysosomal storage disease by administering to said subject a composition comprising a p97 molecule covalently linked to a protein whose deficiency causes said disease. Applicants have elected β-hexosaminidase A to be said protein. Since in the specification, and in the Declaration from Dr. Jeffries filed 28 April 2009, the data presented is on the p97 covalently linked to iduronidase , applicants' claimed species invention is not enabled. Furthermore, Applicants have also admitted on the record that the Applicants' claimed method is an improvement over the art-known prior method of enzyme therapy as the basis to treat lysosomal storage disease. Accordingly, Applicants need to give convincing information with appropriate data that with the administration of the composition claimed in the instantly presented claimed method, the subject administered with said composition was/has been treated of the lysosomal storage disease. Applicants' data, however, shows presence of iduronidase, or p97 in the lysosomal cell *in vitro*, not post administration of a composition comprising p97 covalently linked or fused to β-hexosaminidase A to a **subject** suffering from a lysosomal storage disease. Furthermore, the paragraph 11 of the Declaration from Dr. Jeffries filed 28 April 2009 has discussed fluorescently labeled iduronidase, or fluorescently-labeled p97. There is no linker or fusion in said preparations/compositions. The paragraph 12 and figures in the appendix "J" of the declaration show p97 or iduronidase in the lysosomal cell remaining after

treatment with cathepsin D. The mere presence of said enzyme in the lysosome of a cell *in vitro* does not convincingly give evidence that a subject administered a composition comprising iduronidase covalently linked to p97 has been treated with a lysosomal storage disease, especially in the absence of the evidence that:

- said composition is comprised of a linker as claimed instantly, and
- specific pharmacokinetic data from the subjects having been administered said linker mediated p97 molecule covalently linked to a protein, or to β-hexosaminidase A.

Applicants' arguments filed 28 April 2009 regarding the lack of enablement rejection of Claims 1-5, 7-14 and 16-20 under 35 U.S.C. §112, 1st Paragraph in the Office Action mailed 29 October 2008 have been fully and carefully considered but are not persuasive for the reasons of record at pages 3-6, item 8 in the Office Action mailed 29 October 2008 and those discussed *supra*. Thus, the rejection of Claims 1-5, 7-14 and 16-20 under 35 U.S.C. §112, 1st Paragraph in the Office Action mailed 29 October 2008 is maintained and is adhered to

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

For the aforementioned reasons, no claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Examiner Kailash C. Srivastava whose telephone number is (571) 272-0923. The examiner can normally be reached on Monday to Thursday from 7:30 A.M. to 6:00 P.M. (Eastern Standard or Daylight Savings Time).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon Weber can be reached at (571)-272-0925 Monday through Thursday 7:30 A.M. to 6:00 P.M. The fax phone number for the organization where this application or proceeding is assigned is (571)-273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding may be obtained from the Patent Application Information Retrieval (i.e., PAIR) system. Status information for the published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (i.e., EBC) at: (866)-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Kailash C Srivastava/
Examiner, Art Unit 1657

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31 July 2009

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Primary Examiner, Art Unit 1657